PCT / IN 04/ 00322

INTELLECTUAL PROPERTY **INDIA**
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सत्यमेव जयते

Government Of India
Patent Office
Todi Estates, 3rd Floor,
Lower Parel (West)
Mumbai – 400 013

THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of Application and Provisional Specification filed on 20/10/2003 in respect of Patent Application No.1108/MUM/2003 of Amoli Organics Pvt Ltd., having administrative Office at Plot No.322/4,40 Shed Area, GIDC, Vapi 396 195, Gujarat, An Indian Company.

This certificate is issued under the powers vested in me under Section 147(1) of the Patents Act, 1970.

Dated this 18th day of January 2005.

(R.BHATTACHARYA)
ASST. CONTROLLER OF PATENTS & DESIGNS

FORM 1

THE PATENTS ACT, 1970

(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

[See sections 5 (2), 7, 54 and 135 and rule 33A]

We, (a) Amoli Organics Pvt Ltd. (b) having our administrative Office at Plot no322/4,40 Shed area, GIDC,Vapi 396195, Gujarat and (c) an Indian company,

1. hereby declare –

that we are in possession of an invention titled "Novel Process for preparation of 10-oxo-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide (oxcarbazepine) via intermediate 10-methoxy-5H-dibenz[b,f]azepine-5-carbonyl chloride

(a) that the provisional specification relating to this invention is filed with this application.

(b) that there is no lawful ground of objection to the grant of a patent to us.

2. further declare that the inventors for the said invention are

(a) Full Name: Parenky Chandrashekar
(b) Residential Address: A-11, Happy House, Plot no 16,Sector-9A, Vashi, Navi Mumbai 400703.

(c) An Indian National

and

(a) Full Name: Rohit Chaturvedi
(b) Residential Address: C-10,Saidham CHS, Premier Road, Kurla, Mumbai 400070.

(c) An Indian National

3. We claim the priority from the application(s) filed in convention countries, particulars of which are as follows :

NA

4. We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant/patentee:

NA

5. We state that the application is derived out of our application, the particulars of which are given below and pray that this application deemed to have been filed on 20 October 2003 under section 16 of the Act

1108/MUM/2003
20/10/2003

Duplicate

NA

6. That we are the assignee of the true and first inventors.

Applicable

7. We, the true and first inventors for this invention declare that the applicant(s) herein are our assignee.

(a) Full Name: Parenky Chandrashekar
(b) Residential Address: A-11, Happy House, Plot no 16,Sector-9A, Vashi, Navi Mumbai 400703.

(c) An Indian National

Signature.....
Parenky Chandrashekar

And
(a)Full Name: Rohit Chaturvedi
(b) Residential Address: C-10,Saidham CHS, Premier Road, Kurla, Mumbai 400070.

c) Indian National

Signature.....
Rohit Chaturvedi

8. That our address for service in India is as follow:
Parenky Chandrashekar
Amoli Organics Pvt Ltd
407,Dalamal House,J Bajaj road,
Nariman point,Mumbai,400021

9. Following declaration was given by the inventor(s) or applicant(s) in the convention country:

I/we the true and first inventors for this invention or the applicant(s) in the convention country declare that the applicant(s) herein is/are my/our assignee or legal representative.

NA

11. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

12. Followings are the attachment with the application :

a) Provisional specification (in triplicate). Attached

b) Drawings (sheets) (in triplicate). Nil

c) Statement and Undertaking on FORM -3 (in duplicate). Attached

d) Power of attorney. [To be submitted later]

e) Fee of Rs. 3000 In cheque No.
Date On Bank.

We request that a patent may be granted to us for the said invention.

Dated this Day of 2003.

Pshekar

Parenky Chandrashekar
For AMOLI ORGANICS LTD,

Auth. Signatory/Manager

To
The Controller of Patents
The Patent Office, Mumbai.

FORM 2

THE PATENTS ACT, 1970

(39 OF 1970)

PROVISIONAL SPECIFICATION

(See Section 10)

1. TITLE OF INVENTION

"Novel Process for preparation of 10-oxo-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide (oxcarbazepine) via intermediate 10-methoxy-5H-dibenz[b,f]azepine-5-carbonyl chloride

A) Amoli Organics Pvt Ltd b) having administrative office at Plot no322/4,40 Shed area, GIDC,Vapi 396195, Gujarat c) an Indian Company

The following specification particularly describes the nature of the invention and the manner in which it is to be performed.

Original

1108/MUM/2003

20/10/2003

Field of the Invention

The present invention relates to an improved process for preparation of 10-methoxy-5H-dibenz[b,f]azepine-5-carbonyl chloride from 10-methoxy-5H-dibenz[b,f]azepine (10-methoxy iminostilbene) without the use of phosgene and its further conversion to 10-oxo-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide (oxcarbazepine) without the use of strong mineral acids.

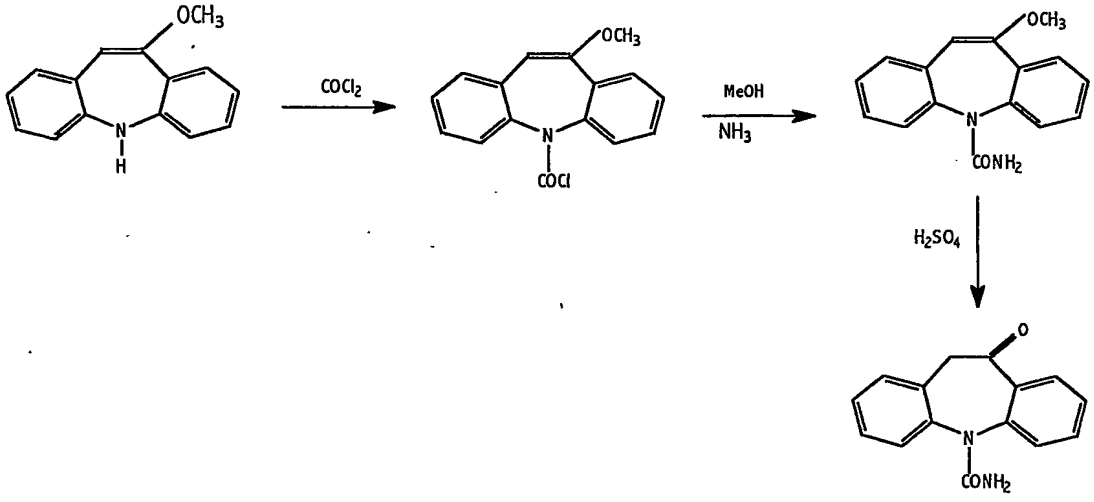
Background and prior art

Oxcarbazepine is an anticonvulsant drug used as an anti-epileptical agent in treatment of AIDS-related neural disorders and for treatment of Parkinson's disease

Several processes for preparing Oxcarbazepine have been reported .

US Patent 3462775 describes the preparation of oxcarbazepine from 10 methoxy iminostibene by phosgenation in toluene, followed by amidation (ethanol and ammonia) and hydrolysis in acidic medium to get the desired product (Scheme 1). The phosgenation is carried out at relatively high temperatures of around 95°C during and the hydrochloric acid produced leads to the formation of undesirable impurities. The process uses phosgene gas, which is toxic and hazardous requiring extreme precaution making this process commercially unattractive.

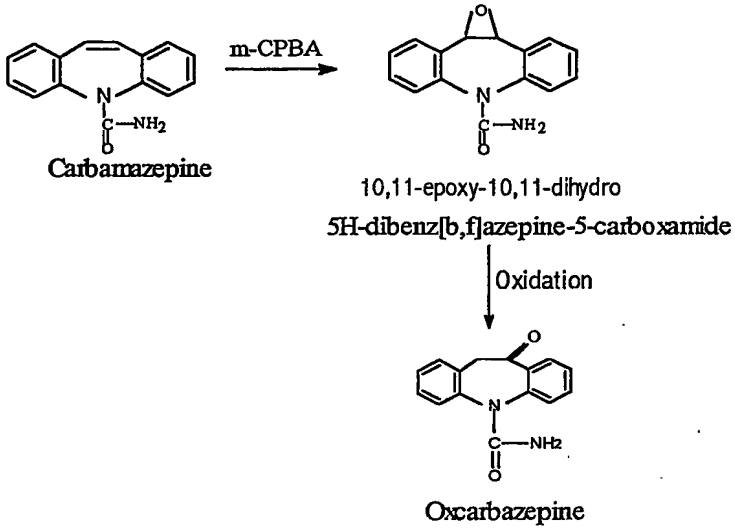
Scheme 1



Oxcarbazepine

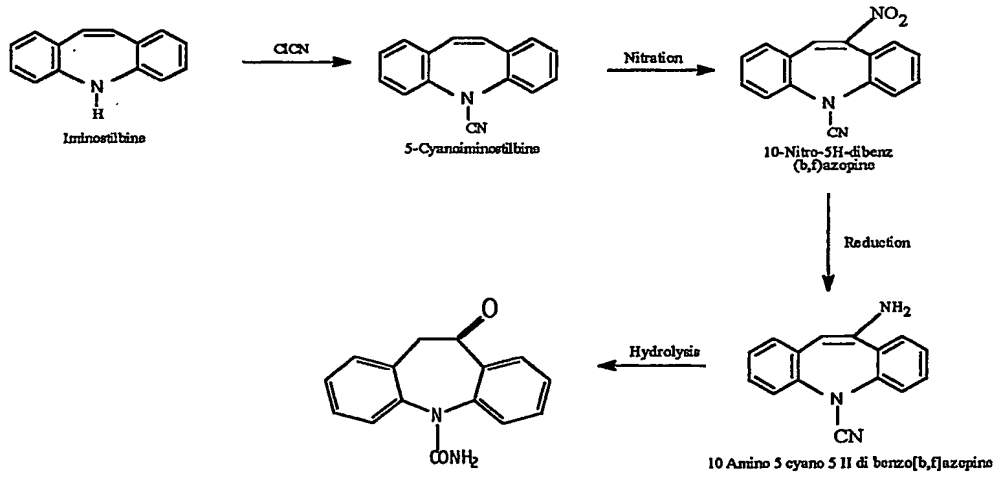
Canadian Patent 112 241 describes an alternate preparation of oxcarbazepine from the catalysed re-arrangement of 10,11-epoxycarbamazepine, prepared from carbamazepine by reaction with m-chloroperbenzoic acid (CPBA) (Scheme-2). Starting with Carbamazepine, which is an expensive raw material, the conversion to its epoxide is poor in quality and yield.

Scheme 2



EP Patent Application 028028, discloses a process involving nitration of 5-cyanoiminostilbene followed by reduction and hydrolysis (Scheme-3). However, the draw back of the process is in the preparation of the 5- cyanoiminostilbene itself, which can be made from iminostilbene and cyanogen chloride. The latter is also toxic, hazardous and difficult to handle.

Scheme 3



Swiss Patent No. 642 950 suggests hydrolysis of the 10-chloro-5H-dibenz [b,f] azepin-5-carboxamide using concentrated sulphuric acid to from the oxcarbazepine. However the yields are poor.

Methods described in the prior art have severe limitations in terms of poor quality and yields and also in some cases with the use of hazardous materials such as phosgene that need extreme care during usage making them commercially unattractive. Moreover the HCl formed during the course of the reaction and the relatively higher temperatures used leads to formation of undesired impurities.

Further it may be noted that in all the processes disclosed in the prior art discussed above (Scheme 1 and Scheme 3) and US Patent 5808058, EP Application 1 302 464 A1 and PCT Publication WO 01/56992A2, the conversion of 10-methoxy-5H-dibenz[b,f]azepine-5-carboxamide to 10-oxo-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide (oxcarbazepine) is effected using strong mineral acids or mixture of mineral acids and acetic acid in aqueous medium. This leads to degradation of oxcarbazepine

The processes described in the prior art become commercially unattractive due to the use of phosgene and mineral acids that lead to degradation of the oxcarbazepine .

There is a long standing need in the industry to provide cost effective, safe and easy operative processes for the production of 10-methoxy-5H-dibenz[b,f]azepine-5-carbonyl chloride from 10-methoxy-5H-dibenz[b,f]azepine (10-methoxy iminostilbene) without the use of phosgene and its further conversion to 10-oxo-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide (oxcarbazepine) without the use of mineral acids.

Summary of the invention

The main object of the invention is to provide a cost effective, safe and high yielding process for the production of 10-methoxy-5H-dibenz[b,f]azepine-5-carbonyl chloride, from 10-methoxy-5H-dibenz[b,f]azepine (10-methoxy iminostilbene) without the use of phosgene gas as is practiced in the prior art an important intermediate for the synthesis of 10-oxo-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide (oxcarbazepine). It is further an object of the invention to provide a process for the conversion of the intermediate 10-methoxy-5H-dibenz[b,f]azepine-5-carboxamide to 10-oxo-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide (oxcarbazepine) without the use of mineral acids.

Another object of the invention is to develop a process that can be conducted at relatively lower temperatures to avoid the formation of any undesirable impurities.

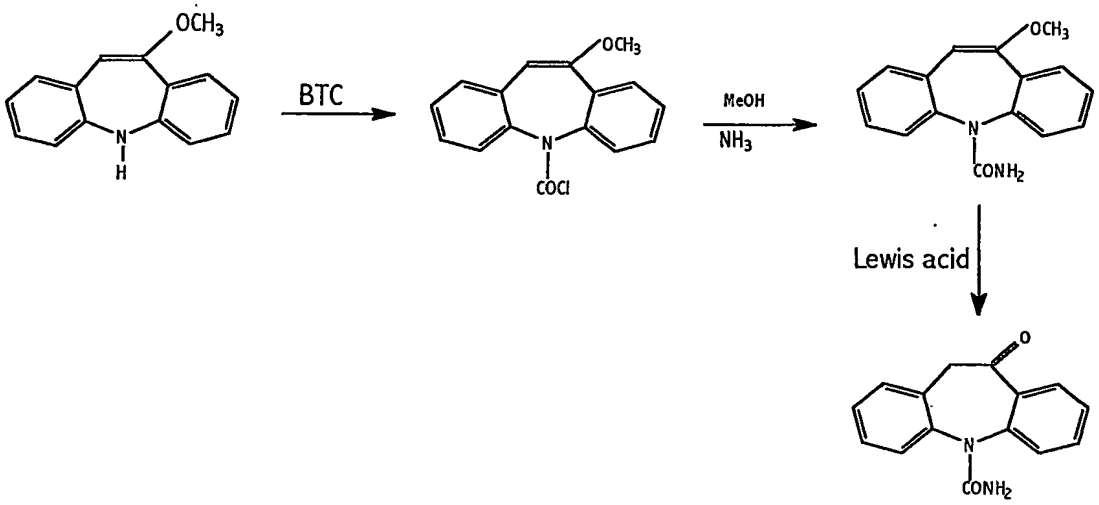
Yet another object of the invention is to provide a cost effective process using easily available raw materials.

Yet another object of the invention is to provide a process for the conversion of the intermediate 10-methoxy-5H-dibenz[b,f]azepine-5-carboxamide to 10-oxo-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide (oxcarbazepine) using mild reagents such as methane sulphonic acid, para toluene sulphonic acid, lewis acids, etc.

We have found that reaction of 10-methoxy imimostilbene with bis-(trichloromethyl) carbonate (BTC) or triphosgene" a solid phosgene substitute equivalent to three moles of phosgene in the presence of an amine in a solvent obviates all the disadvantages of the prior art.

Detailed description of the invention

Scheme 4



Oxcarbazepine

Thus in accordance of this invention the reaction (scheme 4) comprises steps

- Preparation of intermediate 10 Methoxy-5H-dibenz (b,f) azepine-5-carbonyl chloride from 10 methoxyiminostilbine using bis-(trichloromethyl) carbonate (BTC) or triphosgene and an appropriate base in the presence of an organic solvent
- Conversion of 10-Methoxy-5H-di benz (b, f) azepine-5-carbonyl chloride to 10-Methoxy-5H-di benz (b, f) azepine-5-carboxamide using ammonia in a suitable organic solvent

- Formation of oxcarbazepine from 10-Methoxy-5H-di benz (b, f) azepine-5-carboxamide using lewis acids in appropriate organic solvent.

10 methoxyiminostilbene is dissolved in a solvent and cooled below 10 °C and bis- (trichloromethyl) carbonate (BTC) is added. An organic base is slowly added to the above solution over a period ranging from 3-24 hours maintaining the temperature below 10 °C till the reaction goes to completion. Optionally on completion of the base addition the reaction mixture is allowed to warm up to around room temperature and maintained at this temperature till the completion of the reaction as monitored by TLC/HPLC. On completion of the reaction, the reaction mixture is quenched in water and the layers are allowed to separate. The organic layer is separated and distilled to obtain crude 10 Methoxy-5H-dibenz (b,f) azepine-5-carbonyl chloride which is purified using an organic solvent.

In the subsequent step 10 Methoxy-5H-dibenz (b,f) azepine-5-carbonyl chloride is refluxed in an aprotic solvent and ammonia gas is purged till the reaction goes to completion. The solvent is distilled and water is added, cooled to room temperature to isolate the 10-Methoxy-5H-di benz (b, f) azepine-5-carboxamide.

10-Methoxy-5H-di benz (b, f) azepine-5-carboxamide is stirred in an organic solvent in the presence of a lewis acid at temperatures upto 80°C depending on the solvent used. On completion of the reaction the reaction mixture is cooled to room temperature and the crude oxcarbazepine is separated and purified.

The solvent used in the carbonyl chloride preparation step may be selected from chlorinated aliphatic hydrocarbons such as methylene dichloride, chloroform, ethylene dichloride,1,1,1,-trichloroethane,trichloroethylene etc or aromatic hydrocarbon solvent such as toluene, xylene, chlorobenzene, etc. or aprotic solvents including Dimethyl formamide, dimethyl acetamide,N-methyl pyrrolidine and acetonitrile. The organic base used in this step is selected from aliphatic /aromatic tertiary amines such as triethyl amine,dimethyl aniline,pyridine,picoline etc.

In an embodiment of the process initial addition of the base may be followed by the addition of BTC.

The time of the addition of base ranges from 3h –8hrs , the temperature at which the base is added may range upto 30 °C preferably below 10°C and most preferably from 0° To +5° C. The reaction period may vary from about 3 hours to about 10 hours. The molar ratio of 10-methoxy iminostilbene to BTC is 1:0.34-0.5 .The molar ratio of the base 10-methoxy iminostilbene verses the base is 1:1-1.5. The solvents preferred in the amidation reaction are selected from solvents like acetone, methyl cellosolve, methanol, ethanol,isopropyl alchohol dimethyl formamide ,dimethlacetamide,N-methyl pyrrolidone or aromatic solvents like toluene,xylene etc.

The solvent used in the final oxo preparation step may be selected from chlorinated aliphatic hydrocarbons such as methylene dichloride, chloroform, ethylene dichloride,1,1,1,-trichloroethane,trichloroethylene etc or aromatic hydrocarbon solvent such as toluene, xylene, chlorobenzene, etc. or aprotic solvents including dimethyl formamide, dimethyl acetamide,N-methyl pyrrolidine and acetonitrile.

The Lewis acids used in this are selected from methane sulfonic acids,para toluene sulfonic acids, aluminium chloride, etc.
The temperature at which the reaction may be carried out may vary from 25 to 80 ° C, preferably between 50 to 70° C

The invention is now illustrated with a few non-limiting examples.

Example 1

Step 1. Preparation of 10-Methoxy-5H-di benz (b, f) azepine-5-carbonyl chloride

100 gms of 10 Methoxy iminostilbene is dissolved in 300 ml chloroform & cooled to 0 °C. Bis (trichloro methyl) carbonate (BTC) 65 gms is added. 67 gms of triethyl amine (TEA) in 100 ml chloroform is added slowly over a period of 6 hour maintaining the temperature 0 - 5 °C. Temperature is then increased to 25-30 °C & maintained for 8 hour. The reaction mixture is poured into 300 ml water & layers are separated. Chloroform is evaporated & 10-Methoxy-5H-di benz (b, f) azepine-5-carbonyl chloride is isolated in methanol. Yield obtained is 110 gms (86%) of theoretical.

Step 2. Preparation of 10-Methoxy-5H-di benz (b, f) azepine-5-carboxamide from 10-Methoxy-5H-di benz (b, f) azepine-5-carbonyl chloride

100 g of 10-Methoxy-5H-di benz (b, f) azepine-5-carbonyl chloride is refluxed in 500 ml methanol.. Dry ammonia is passed into the boiling solution for 2 hours. The methanol is distilled water added and the reaction mixture is cooled to 25-30 °C and filtered. Yield of 10-Methoxy-5H-di benz (b, f) azepine-5-carboxamide is 82 g.

Step 3 Preparation of oxcarbazepine from 10-Methoxy-5H-di benz (b, f) azepine-5-carboxamide

85 gm of 10-Methoxy-5H-di benz (b, f) azepine-5-carboxamide is dissolved in 425 ml of ethylene dichloride .To this 800 ml of 2 N Sulphuric acid is added and heated to 75-80 °C & maintained for about 3 hours . It is then cooled to 20 °C & maintained for about 1 hour. The product oxcarbazepine is separated by filtration. This is then purified in acetone-water to yield 55 gms of pure oxcarbazepine.

Example 2

Step 1. Preparation of 10-Methoxy-5H-di benz (b, f) azepine-5-carbonyl chloride

100 gms of 10 Methoxy iminostilbine is dissolved in 300 ml chloroform & cooled to 0 °C. 65 gms of Bis (trichloro methyl) carbonate (BTC) is added to the solution followed by the addition of 54 gms of Dimethyl aniline in 100 ml chloroform over a period of 4 hours maintaining the temperature 0-5 °C. The temperature is then maintained0-10 °C & maintained for 2 hour. The reaction mixture is poured into 300 ml water & layers are separated. Chloroform is evaporated & product is isolated in methanol. Yield obtained is 104gms (82%) of theoretical.

Example 3

Step 1. Preparation of 10-Methoxy-5H-di benz (b, f) azepine-5-carbonyl chloride

100 gms of 10 Methoxy iminostilbene is dissolved in 300 ml chloroform & cooled to 0 °C and 45 gms Bis (trichloro methyl) carbonate (BTC) is added followed by the addition of 45 gms of TEA in 100 ml chloroform over a period of 8 hours maintaining the temperature at 0-5 ° C. The temperature is then increased to 25-30 °C & maintained for 2 hours. The reaction mixture is poured into 300 ml water & layers are separated. Chloroform is evaporated & product is isolated in methanol. Yield obtained is 100 gms (80%) of theoretical.

The present invention obviates the use of phosgene gas in the preparation of 10-methoxy-5H-dibenz[b,f]azepine-5-carbonyl chloride from 10-methoxy-5H-dibenz[b,f]azepine (10-methoxy iminostilbene). Further the invention provide a process for the conversion of the intermediate 10-methoxy-5H-dibenz[b,f]azepine-5-carboxamide to 10-oxo-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide (oxcarbazepine) without the use harsh conditions and strong mineral acids thereby obtaining high quality oxcarbazepine in a cost effective manner from easily available raw materials.

For AMOLI ORGANICS LTD,
Applicant

Auth. Signatary/Manager

Date:20 October, 2003

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Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse